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*Original Research*

# Evaluation of the effectiveness of different hemostatics and bioactive materials on the success of vital pulp therapy

Evaluation of materials using in pulp therapy

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**Abstract**
Aim: The aim of this study was to evaluate the response of the pulp in combination of hemostatic agents with pulp capping materials (PCMs).
Material and Methods: A total of 96 rats were used. Two molar teeth of each rat were included and all groups were created of 4 animals. In the occlusal cavities of the teeth, pulp perforations were performed for direct pulp capping. Thereafter, three different agents, which were forming the main groups [Group1: Sterile saline, Group2: Sodium hypochlorite, Group3 :Mecsina Hemostopper] at different periods of time used on pulp perforations  and according to PCMs coated on the exposed pulp area, were divided into subgroups (Dycal, Biodentine, Theracal, and MTA Repair HP). Subsequently, all groups were left for two different waiting periods of 7 and 28 days. Half of the rats were sacrificed on the 7th and the remaining half were sacrificed on the 28th day, followed by micro-CT and histological analyzes.
Results: When the results of the study were examined, a statistical difference was observed between groups in terms of dentine bridge (DB) formation on the 7th and 28th days, while there was no statistical difference between inflammatory cell response and DB quality. Micro-CT images showed no formation of DB on the 7th day, while DB formation was observed on the 28th day on specimens.
Discussion: The combination of MHS and NaOCl may be preferable in order to provide pulp bleeding control in dental applications.

**Keywords**
Bioactive Materials, Direct Pulp Capping, Hemostatic agents, Histology, Micro-CT

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## Introduction

Direct pulp capping (DPC) is a process of direct covering of the pulp tissue with a tissue-friendly material that stimulates the repair of dentine and maintains the viability of the pulp. After the perforation, bleeding occurs in the capillaries under the pulp tissue. The amount of hemorrhage is proportional to the number of damaged vessels and the size of the wound surface opened [1]. It has been argued that after waiting for hemostasis, the most frequently applied treatment method, in which accumulated blood is removed with SS, may cause problems such as dislocation of the clot and reactivation of hemorrhage, and may also stimulate pulp inflammation [2].

The use of a hemostatic agent (HA) is recommended to promote the formation of the blood clot during hemorrhage control in the pulp for treatment of the vital pulp [3]. For the control of pulp hemorrhage, some solutions such as sodium hypochlorite (NaOCl) solution, sterile saline (SS) 2% chlorhexidine, hydrogen peroxide and electro-surgery etc. were used in many studies [4]. In addition, are the main reasons for the preference of this HA are the following: it has a good solvent effect against organic wastes, it is an antiseptic, it has low surface tension, it is easy to find and cheap [5].

Mecsina hemostopper (MHS) as a herbal agent includes 46% vitis vinifera extract, 16% hypericum perforatum extract, 12% glycyrrhiza glabra extract, 8% urtica angustifolia extract, 6% mentha arvensis juice, 5% alpinia officinarum extract, 4% syzygium aromaticum extract, and 3% thymus serpyllum extract. It can be used in liquid form in dentistry.

Although many biocompatible materials were developed for use in the DPC procedure, Ca(OH)2 is still considered the gold standard for comparing and evaluating the success of these newly produced products [6]. Theracal, Biodentine and MTA Repair HP are known as bioactive endodontic, and tricalcium silicate-based materials have been used as DPC materials in the present study. It is stated that an ideal bioactive endodontic material (BEM) in dentistry should be bactericidal, bacteriostatic, biocompatible, stimulating hard tissue formation and preserving

pulp vitality. It is also reported that a BEM should prevent tissue inflammation and tissue degeneration and stimulate the healing process [7]. A new bioactive material, MTA Repair HP, is manufactured in the form of a high-plasticity bioceramic material, which aims to preserve the biological properties of traditional ProRoot MTA as well as improve its chemical and physical properties.

The aim of this study is to investigate the pulpal response to 3 different HAs with 3 different pulp capping materials using micro-CT and histological imaging. The null hypothesis of the present study is that the pulpal response did not differ in the application of the HAs with different capping materials.

## Material and Methods

This research was approved by the Ethics Commission of the University Animal experiments (ID: 65202830-050.04.04-188). A total of 96 Wistar male albino rats (200-220 gr) were used in the study. All experiments were conducted in compliance with the National Institute of Health's Guidelines for the Care and Use of Laboratory Animals and in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Subjects were kept in standard test cages at 22-24 °C, 55-70% humidity, 1 atm pressure for 12 hours in a light/dark room and their health status was checked.

***Animals***

The animals have been anesthetized with ketamine HCL (25 mg/kg) and xylazine (10 mg/kg). After anesthesia, the mouths of the animals were cleaned from food residues and existing extraneous attachments, and the working place was disinfected with the batticon. A total of 192 molar teeth of the 96 rats, including the upper jaw right and left first molars of each rat.

***Pulp Capping Procedure***

***Main groups were formed according to the type of hemostatic agents (HAs):***

*Group 1: 0.9% Sterile saline (SS)

**Group 2: 5% NaOCl (group 2)

***Group 3: Mecsina Hemostopper (MHS)

Class 1 cavities were formed from the occlusal surface with diamond round burs to the first molar teeth of the rats. After cavity preparation, the pulp perforations were performed with sharp dental explorers. The hemostatics impregnated cottons were applied to the pulp perforated area. The groups were then divided into 1 week and 4 weeks (n = 8) according to type DPC material.

In Groups 1, 2 and 3, following the application of the HAs, application procedures of DPC materials (Dycal(a), Biodentine(b), Theracal(c), MTA Repair HP(d)) were performed according to the manufacturers' recommendation (Table 1).

After 7 and 28 days of periods, the sacrification procedures were performed. In order to observe the formation of dentine bridge (DB) in the pulp, the teeth were imaged with micro–computed tomography (Micro-CT). After micro-CT imaging, histological hematoxylin- eosin examinations were performed to examine the inflammation cell response, DB formation in the pulp and the quality of the hard tissue formation. The histological evaluation criteria are shown in Table 2.

***Micro-Computed Tomography***

The fixed block sections were scanned using a micro-CT machine (SkyScan1172 version 1.5; Bruker Micro-CT, Kontich, Belgium). Each section was mounted in the middle of the specimen platform and scanned at 80 kV and 124 µA with a resolution of 13.68 µm, frame averaging 3, rotational step of 0.6°, and 180° rotation using 0.5-mm aluminum filters and 54% beam hardening reduction average scan time was 45 min. Raw data were reconstructed with NRecon Software version 1.6.4.8 (Bruker Micro-CT) to obtain rough measurements of the newly formed DB. Because of the contribute a precise and certain images of each sample and allowed measurements of the DBs, Data Viewer software version 1.4.4 was used to obtain 3 distinct views (coronal, sagittal, and transaxial) of each image in 2-dimensional form. Raw data were analyzed with CT analyzer (CTan) Software version 1.11.10. Two-dimensional slices were acquired in the axial plane to determine the first and last images in the coronal-to-apical direction from which newly formed DB could be assigned from the pulp.

***Histological Analysis***

For the histological analysis, the samples were decalcified in 10% formic acid after being fixed in 10% formalin solution and embedded in paraffin blocks. Five micron sections were obtained from samples embedded in paraffin blocks and each section was stained with hematoxylin- eosin. Histological preparations were examined by a pathologist (F.G) under a light microscope (Eclipse E 600, Nikon, Tokyo, Japan) at 100X magnification.

*Statistical Analysis*

The data were analyzed using SPSS 22.0. Kruskal-Wallis and Mann-Whitney U tests were used for the statistical analysis of the data. A p-value <0.05 was accepted statistically significant.

## Results

*Micro-CT Analysis*

Four samples were randomly selected from each group for micro-CT analysis. Micro-CT images, reconstructed in the sagittal plane, showed DB formation 28 days after pulpotomy (Figure 1).

The highest and lowest average volumes of DBs were recorded in Group 3b (10,7x10-3mm3) and Group 1a (2,1 x 10-3 mm3), respectively (Table 3). While the highest DB volume was seen in MHS group (7,8x10-3mm3), the lowest bridge formation volume was shown in Group 1 (2,9x10-3mm3).

*Hard tissue formation*

When the values of the 1st and 4th weeks were evaluated in terms of DB formation among all groups, the scores were found to be statistically significant (p<0.05). No hard tissue formation was observed in some samples of the SS and NaOCl groups (1A-

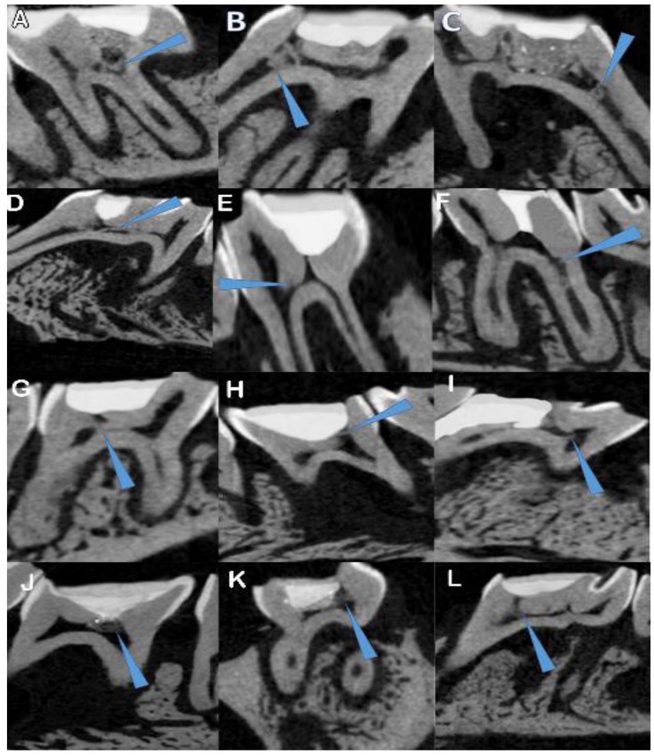


**Figure 1.** Micro-CT images of DB at 28th days. Biodentine[(A:SS,B:NaOCl,C:MHS],Dycal [D:SS, E:NaOCl, F:MHS], MTA Hp[(G:SS, H:NaOCl, I: MHS], Theracal :[J:SS, K:NaOCl, L:MHS]

**Table 1.** DPC Materials used in the study

| Material/Lot number | Components | Manufacturer |
|---|---|---|
| Dycal/160523 | Two-paste system made of a base paste (1,3-butylene glycol disalicylate, zinc oxide, calcium phosphate, calcium tungstate, iron oxide pigments) and a catalyst paste (calcium hydroxide, N-ethyl-o/p-toluene sulphonamide, zinc oxide, titanium oxide, zinc stearate, iron oxide pigments) | Dentsply, Caulk Milford, DE, USA |
| Biodentine/B21369 | Powder containing tricalcium silicate, calcium carbonate and zirconium oxide. Liquid containing water, calcium chloride (accelerator) and modified polycarboxylate | Septodont, Saint Maur des Faussés, France |
| Theracal LC/1700001689 | Light-curing, resin-modified calcium silicate filled liner single paste containing CaO, calcium silicate particles (type III Portland cement), Sr glass, fumed silica, barium sulphate, barium zirconate and resin containing Bis-GMA and PEGDMA | Bisco Inc, Schamburg, IL, USA |
| MTA Repair HP/40836 | Powder containing tricalcium silicate, Dicalcium silicate, Tricalcium aluminate, Calcium oxide, and Calcium tungstate, Liquid containing water and polymer plasticizer | Angelus, Londrina, PR, Brazil |

**Table 2.** Criteria Used for the Histologic Analysis after Direct Pulp Capping

| Grade | Hard Tissue Formation | Inlammatory Cell Response | Quality of Dentine Formation in the Bridge |
|---|---|---|---|
| 1 | Heavy: hard tissue deposition as complete and continuous dentine bridge | Absent or few inflammatory cells | Regular pattern of tubules |
| 2 | Moderate: hard tissue formation as incomplete and discon-tinuous dentine bridge | Mild: inflammatory cells only next to dentine bridge or area of pulp exposition | Irregular pattern of tubules |
| 3 | Slight: a layer of scattered and foggy hard tissue deposition | Moderate: inflammatory cells are observed in the part of coronal pulp | No tubules present |
| 4 | No hard tissue deposition | Severe: all coronal pulp | - |

**Table 3.** Micro-CT mean values of groups

| Grade | Hard Tissue Formation | Inlammatory Cell Response | Quality of Dentine Formation in the Bridge |
|---|---|---|---|
| 1 | Heavy: hard tissue deposition as complete and continuous dentine bridge | Absent or few inflammatory cells | Regular pattern of tubules |
| 2 | Moderate: hard tissue formation as incomplete and discontinuous dentine bridge | Mild: inflammatory cells only next to dentine bridge or area of pulp exposition | Irregular pattern of tubules |
| 3 | Slight: a layer of scattered and foggy hard tissue deposition | Moderate: inflammatory cells are observed in the part of coronal pulp | No tubules present |
| 4 | No hard tissue deposition | Severe: all coronal pulp | - |

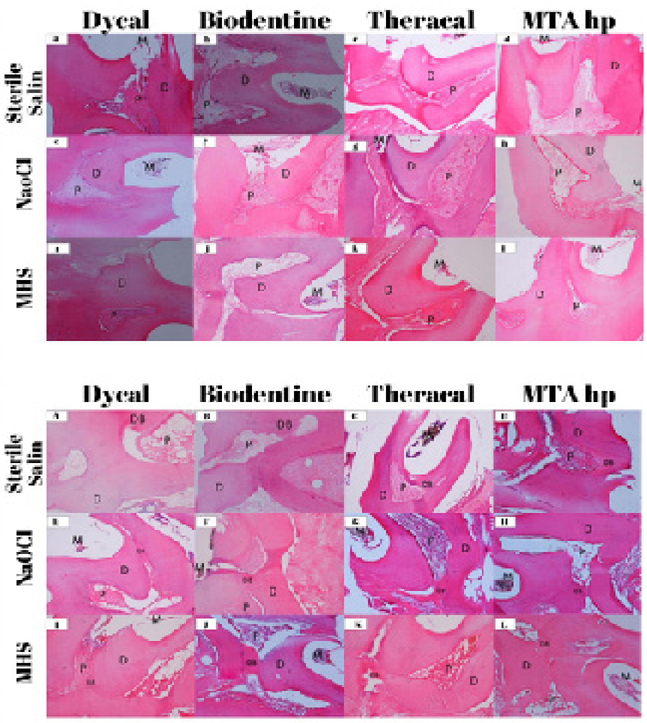


**Figure 2.** Images on day 7 are indicated with a lower letter. (a:dycal, b:Biodentin, c:theracal, d: MTA Repair Hp). Images on day 28 are indicated with a capital letter (A:dycal, B:biodentin, C:theracal, D:MTA Repair Hp). D, Dentine; P, Pulp; M, Material; DB, Dentine bridge. All images were obtained with 100x magnification.

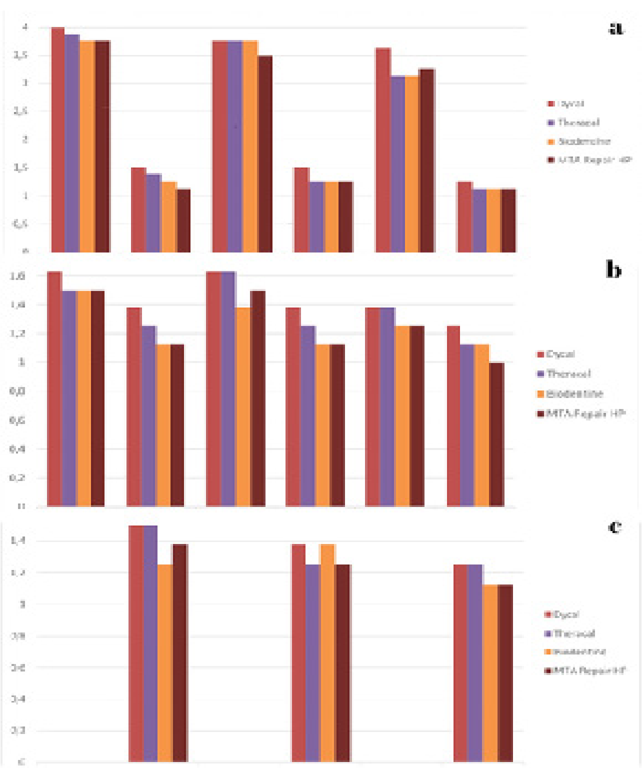


**Figure 3.** Hard tissue formation scores on the 7th and 28th days (a). Inflammatory cell response scores on the 7th and 28th days (b). Quality of dentine formation in dentine bridge score of different hemostatics in 28th day (c).

D; 2A,B) at week 1 (Figure 2A-F). When the histological images of the 1st week were evaluated, incomplete dentine bridge and irregular hard tissue formation were observed in NaOCl and MHS groups (2C, D; 3A-D) in Figure1 (G-L). However, in all groups at 1 week, the statistical difference was insignificant ($p > 0.05$).

While incomplete DB appearance was shown in the Dycal group at the 4th week, , regular DB formation was observed in many of the samples treated with NaOCl and MHS (Groups 1a-d, 2a-d, 3a) in Figures 2a-i. At 28 days, the best scores according to DB scoring were seen in MHS+Biodentine, MHS+Theracal and MHS+MTA HP groups (Figures 2B, C, D). However, in all groups, the difference obtained on the histological images of the 4th week in terms of DB formation was not statistically significant ($p > 0.05$). When DB formation was evaluated at week 4, regular tubular structure was observed, but this formation was not found to be statistically significant between all groups ($p > 0.05$) (Figure 3a).

***Inflammatory Cell Response***

When the 1st-week values were evaluated, the highest inflammation scores were seen in SS+Dycal, NaOCl+Dycal and NaOCl+Theracal (1,63) groups, while the lowest inflammation scores were found in MM and BM (1.25) groups, and the statistical difference between the groups was insignificant ($p > 0.05$). When the inflammation values of the 4th week were examined, although there was a decrease in the inflammation scores in all the groups, the statistical difference between the groups was insignificant ($p > 0.05$). When the inflammation scores at the 1st and 4th weeks were compared, the difference has been found to be statistically insignificant ($p > 0.05$) (Figure 3a).

***Quality of dentine formation in dentine bridge***

When the quality of DB in the 4th week was evaluated between the groups, no statistical difference was observed between the groups. The difference between the groups was found to be statistically significant ($p < 0.05$) in terms of DB formation between the 1st week and 4th week, but the difference in inflammation cell response was found to be statistically insignificant ($p > 0.05$) (Figure 3b).

## Discussion

The 30-day life cycle of rats has been shown to be equal to the 30-month life cycle of human beings, and it has been reported that the response of pulpal injury in rat molar teeth is observed on the fifth day after injury [8]. However, as the highest level of pulpal response has occurred on days 5 and 6 and as the formation of tertiary dentine, depending on the severity of the injury, has actualized on days 7-35, we preferred the observation intervals of the 7th and 28th days in present study [9].

Sterile saline (SS) is known to be the most conventional hemostatic material used in clinical practice to provide bleeding control in DPC. However, its long waiting period in clinical applications, the difficulty experienced in patient cooperation and difficulty in providing isolation have led clinicians to use alternative hemostatic agents. In the present study, NaOCl, which has a shorter clinical application time (20 sec), and MHS, which is a newly-introduced herbal material were applied during the pulpal treatment.

Long et al. have used different pulp capping materials in the treatment of rats [10]. They have examined the pulp inflammation cell response, hard tissue formation, and dentin bridge quality in the 1st and 4th weeks. They reported that there was no statistically significant difference between the 1st and 4th weeks in terms of inflammatory cell response and dentin bridge quality, but there was a significant difference between the 1st and 4th weeks in terms of hard tissue formation. These results were found to be similar to those we obtained in the present study.

Sodium hypochlorite (NaOCl) is used in the treatment of pulp at different concentrations (3-5%) and durations (30-80 sec) as a hemostatic agent [11,12]. In the present research, NaOCl was applied at a concentration of 5% for 20 seconds to control pulpal hemorrhage. The mechanism of action of herbal-based MHS, another hemostatic agent we use in the study, is to provide the formation of erythrocyte aggregation through encapsulated protein network formation [14,15]. MHS is limited in studies when the literature review is made. MHS provides its hemostatic activity by increasing the amount of vascularization by clot formation from erythrocytes.

Ankaferd blood stopper (ABS) containing herbs similar to MHS, used in present study, reduces the prevalence of inflammation [16]. This research has shown similar results for the inflammation criteria compared with the present study.

In clinical pratice, Dycal is an ideal pulp capping material, it has been criticized and controversial for tunnel defects in the bridge it forms [19,20]. In addition, the unstable physical properties of the calcium hydroxide allow particles of this material to migrate to the pulp, which can lead to necrosis [19]. TheraCal LC, which was the other material used in the study, was similar to Biodentine and MTA HP because it contains tricalcium silicate, but its hardening with light provides an advantage in terms of ease of use. Biodentine is highly preferred in children and adults due to its good physical and mechanical properties such as high tightness and stimulation of tertiary dentin production.

MTA Repair HP, an agent within MTA group, exhibited high plasticity and ease of manipulation, and these properties have been effective in choosing this material because of the advantage of a permanent restoration in one session, and also because there is no study available on dental pulp in the literature. Benetti et al. have concluded that histologically compared traditional MTA and MTA Repair HP materials are biocompatible and trigger biomineralization. They also have reported that the inflammatory response was moderate and low at 7 and 30 days [20]. In the present study, inflammatory responses have been found to be similarly low in the groups treated with MTA Repair HP.

Histological images are often used to evaluate the healing process in many pulp capping studies. It has been emphasized that quantitative evaluations of thin sections are not very reliable due to the idea that histological sections may cause non-objective interpretations [24]. Okamoto et al. have stated that there is a significant increase in the density of tertiary dentine in the 4th week in their study in which they have used ProRoot MTA and iRoot BP materials and evaluated with micro-CT [21]. There was a significant increase in dentine density between the groups in the 1st and 4th weeks, similar to the present study. Micro-CT imaging method is a non-invasive procedure and has recently been used in pulp studies for morphological evaluation [22]. We have chosen to use both histological and micro-CT imaging methods in this study.

Studies on human and animal models have shown that MTA is more effective than the other materials in the formation of tertiary dentine [23]. In the groups where the pulp hemostasis is controlled with NaOCl and with especially MHS, dentine bridge formation with an irregular tubule structure has been observed on histological image samples after 1 week. Regardless of the differences in DPC materials, in the histological sections, tubular structure was found to be more regular in the MHS-treated group in terms of hard tissue formation scoring. Since MHS and MTA Hp materials have been used on pulp in-vivo for the first time in literature, we believe that this study will guide and contribute to new clinical studies. Thereafter, clinical studies on human pulp are needed.

The present study showed that bleeding control could be safely achieved in a short period of 20 sec by using NaOCl and herbal-based material MHS. We also think that the combined use of these NaOCl and MHS with newly developed bioactive endodontic materials will increase the success of direct pulp capping. We believe that the use of hemostatic agents (NaOCl and MHS) that provide hemorrhage control in such a short period of time, especially in pediatric patients, will help pediatric dentists in the clinic.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

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***Conflict of interest***

*None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.*

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